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Conjugate addition of indoles and thiols with electron-deficient olefins catalyzed by $Bi(OTf)_3$

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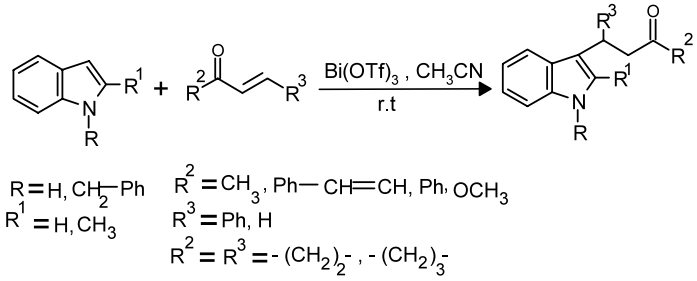
Abstract—Conjugate addition of indoles and thiols with a variety of electron-deficient olefins mediated by a catalytic amount of $Bi(OTf)_3$ at ambient temperature to afford the corresponding Michael adducts in good to excellent yields with high selectivity is reported.

Addition reactions of indoles and thiols to electron-deficient olefins have received much interest because a number of their derivatives occur in nature and possess a variety of biological activities.[1] Since the 3-position of indole is the preferred site for electrophilic substitution reactions, 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives.[2] A simple and direct method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of either protic[3] or Lewis acids.[4] However, the acid-catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions such as dimerisation or polymerization. Furthermore, many of these procedures involve strongly acidic conditions, expensive reagents and long reaction times, give low yields of products due to dimerisation of the indoles or polymerization of the vinyl ketones, and involve cumbersome experimental product isolation procedures. There is a need for cheaper and more efficient Lewis acid catalysts for Michael-type addition reactions. In this regard, bismuth triflate has been found to be useful to organic chemists.

Recently, bismuth triflate has emerged as a powerful Lewis acid for various chemical transformations.[5] We have reported that bismuth triflate can be used as an



Scheme 1.

Keywords: $Bi(OTf)_3$; indoles; thiols; α,β-unsaturated compounds; addition reactions.

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excellent catalyst in the Biginelli reaction under mild conditions.[6] Herein, we describe the remarkable catalytic activity of $Bi(OTf)_3$ in the conjugate addition of indoles and thiols to α,β-unsaturated compounds (Schemes 1 and 2).[7]

We were pleased to find that indole smoothly reacted with methyl vinyl ketone in the presence of a catalytic amount of $Bi(OTf)_3$ (5 mol%) in acetonitrile to give the corresponding 3-alkylated product in 90% yield after 1.5 h at ambient temperature (entry 4, Table 1). Encouraged by this result, we carried out the reaction under different conditions and the results were satisfactory. The best solvents for this reaction were found to be dichloromethane, dichloroethane, water, THF and acetonitrile. Acetonitrile was a much better solvent in terms of yields than all the other solvents tested. The use of 5 mol% of bismuth triflate was sufficient to carry out the reaction. Substituted and unsubstituted indoles were used in the optimized procedure. 2-methylindole (entry 2, Table 1) furnished higher conversions in comparison to other indoles (entries 1 and 3, Table 1).

The reaction seems to occur via a Friedel–Crafts alkylation pathway.[8] It is interesting to compare several of the entries from Table 1. Electron-deficient olefins such as methyl vinyl ketone, phenyl vinyl ketone, dibenzylidene acetone, afforded the products in good to excellent yields. Other Michael acceptors such as vinyl cyanide and methyl acrylate also reacted well under these conditions.[4a,e] In the case of dibenzylidene acetone, no bis-alkylated product was observed (entry 6, Table 1). The treatment of β-nitrostyrene with indole produced the corresponding 3-alkylated indole (entry 7, Table 1) in excellent yield. The NH proton of the indole does not play a significant role in the formation of the addition product (entries 3 and 8, Table 1). The reactions were clean and the products were obtained in high yields without the formation of any side products such as dimers or trimers, which are normally observed under the influence of strong acids. The procedure does not require any acidic promoters or anhydrous conditions.

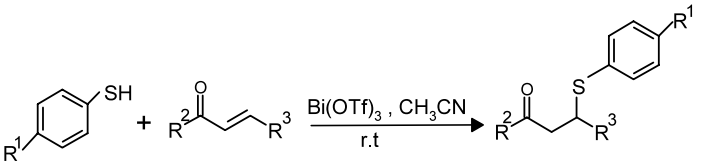
Conjugate addition of thiols to α,β-unsaturated ketones catalyzed by $Bi(OTf)_3$: the 1,4 addition of thiols to electron deficient olefins to form a carbon–sulfur bond constitutes a key reaction in biosynthesis as well as in the synthesis of biologically active compounds such as the calcium antagonist diltiazem.[9] In the literature, a large number of conjugate additions based on the activation of thiols by bases have been reported.[10] In contrast, only a few reports on the addition of thiols by activation of the acceptors with Lewis acids are known.[11] Additions of sulfur nucleophiles to α,β-unsaturated ketones have now been carried out by the use of $Bi(OTf)_3$ (Scheme 2).[7] Substituted and unsubstituted aromatic thiols can be used in the optimized procedure with numerous cyclic and acyclic ketones. Products were isolated in good yields after column chromatography and the results are summarized in Table 2. Benzylmercaptan (entry 3, Table 2) afforded a higher conversion in comparison with other thiols (entries 1 and 2, Table 2). In the case of dibenzylidene acetone, the bis-alkylated product was observed under these reaction conditions (entries 10 and 11, Table 2).

In general, thiols reacted faster than indoles with electron deficient olefins under the present reaction conditions.

In summary, we have demonstrated $Bi(OTf)_3$ as a superior Lewis acid for the alkylation of indoles and thiols with electron-deficient olefins.

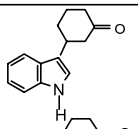
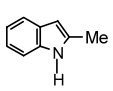
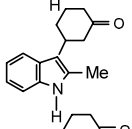
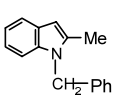
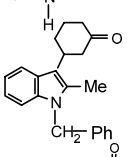
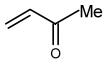
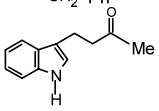
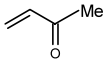
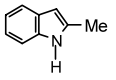
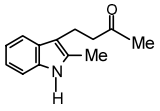
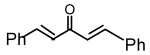
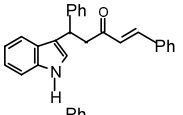
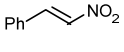
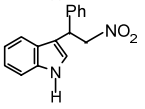
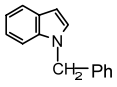
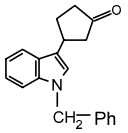
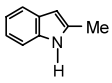
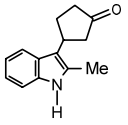
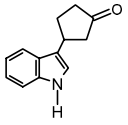
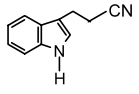
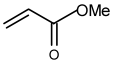
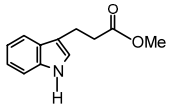
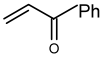
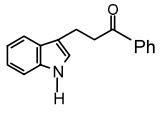
Acknowledgements

M.M.A. and V.R thank Dr. B. M. Choudary, Head of the Division and the Director, Dr. K. V. Raghavan for their constant support throughout the work.



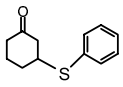
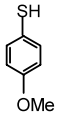
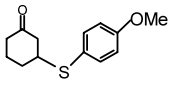
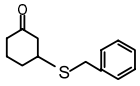
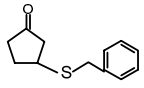
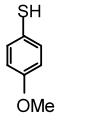
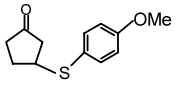
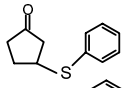
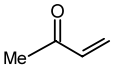
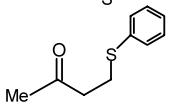
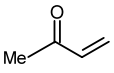
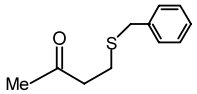
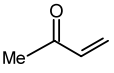
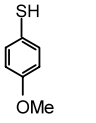
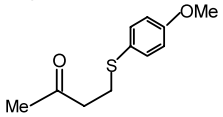
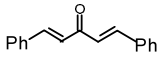
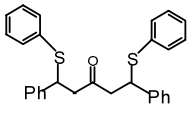
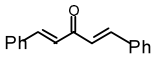
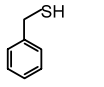
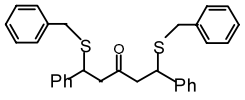
Scheme 2.

Table 1. Michael addition of indoles with electron-deficient olefins catalyzed by $Bi(OTf)_3$

Entry	Electrophile	Nucleophile	Product[a]	Time (h)	Yield (%)[b]
1				1.5	87
2				1.0	92
3				1.5	65
4				1.5	90
5				1.0	95
6				2.5	75
7				2.5	80
8				3.0	60
9				2.0	80
10				2.5	70
11				5.0	60
12				4.5	62
13				2.5	82

[a] All products were characterised by ^1H NMR, IR and mass spectroscopy.
[b] Isolated yields after column chromatography.

Table 2. Michael addition of thiols with electron-deficient olefins catalyzed by $Bi(OTf)_3$

Entry	Electrophile	Nucleophile	Product[a]	Time (h)	Yield (%)[b]
1				1.5	72
2				1.0	70
3				0.5	85
4				0.5	82
5				0.5	78
6				1.0	75
7				1.0	70
8				1.0	85
9				0.5	75
10				3.0	60
11				2.5	65

[a] All products were characterised by ^1H NMR, IR and mass spectroscopy.
[b] Isolated yields after column chromatography.

References

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7. **General procedure for the catalytic addition of indoles and thiols to α,β-unsaturated ketones**: A mixture of indole or thiol (0.45 mmol), α,β-unsaturated carbonyl compound (0.3 mmol), and $Bi(OTf)_3$ (5 mol%) in acetonitrile (5 ml) was vigorously stirred at ambient temperature for the appropriate time (Table 1 or Table 2). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure, and the crude mixture was purified by column chromatography to obtain the pure product.
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